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EXAMINER	
VAKILI, ZOHREH	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

PTOL-90A (Rev. 04/07)

Office Action Summary	**Application No.** 10/677,747	**Applicant(s)** ZHANG ET AL.
	Examiner Zohreh Vakili	**Art Unit** 1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.
2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.
3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3 and 18-50* is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5)☐ Claim(s) _____ is/are allowed.
6)☒ Claim(s) *3 and 18-50* is/are rejected.
7)☐ Claim(s) _____ is/are objected to.
8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.
10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a)☐ All b)☐ Some * c)☐ None of:
1.☐ Certified copies of the priority documents have been received.
2.☐ Certified copies of the priority documents have been received in Application No. _____.
3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :5/13/2004, 5/14/2007, 06/04/2007.

DETAILED ACTION

Claims 3, 18-50 are presented for examination.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 29, 2007 has been entered. Claims 1-2, and 4-17 are cancelled. Claims 3, 18, 27, 45, 49, and 50 are currently amended.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 3, 18-50 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thompson et al. (U.S. Patent No. 7034013 B2) in view of Chen et al. (US Patent No. 6383471 B1).

Thompson et al. teach an injectable formulation of a sedative hypnotic drug, such as the anesthetic drug **propofol**, that is pharmaceutically stable and demonstrates a reduced incidence of pain upon injection. The formulation of the present invention employs a sulfoalkyl ether cyclodextrin solubilizing and complexing excipient, such as CAPTISOL.RTM. cyclodextrin (sulfobutyl ether beta.-cyclodextrin) to form a true aqueous solution and not a suspension. This formulation minimizes the allergic response and microbial contamination issues typically associated with propofol parenteral formulations. The present formulation may also reduce pain on injection as compared to the known emulsion type propofol formulations. The liquid formulation can be sterile filtered unlike emulsion-type formulations of sedative hypnotics. The liquid formulation can be lyophilized or otherwise dried to yield a solid formulation (see abstract). Specific embodiments of the present formulation are substantially **lipid-free**, or they can contain no lipid (see col. 25, lines 46-48). The liquid formulation of the invention can be provided in an ampoule, syringe, bottle, vial or other such container typically used for parenteral formulations, reads on claim 50 (see col. 25, lines 50-52). The formulation of the invention can also include water, organic solvent(s) and combinations thereof. In particular embodiments, the formulation includes alcohol, water, and saline. Specific embodiments of the invention include pyrogen-free, sterile water as liquid carrier. The water can comprise other components described herein. Water suitable for injection is suitable for use in the liquid formulation of the invention (see col. 21, lines 38-46). The formulation of the invention can also include biological salt(s), sodium chloride, potassium chloride, or other electrolyte(s) (see col. 22, lines 47-49). The chemical stability of the liquid formulations of the invention, in terms of the formation of the above-mentioned dimer, can be enhanced by: adding an antioxidant, adjusting the pH of the liquid carrier, and/or eliminating or minimizing the presence of oxygen in the formulation. The chemical stability can also be enhanced by converting the liquid formulation to a solid formulation, (see col. 22, lines 51-57). Generally, the least amount of propofol degradation (least amount of dimer formation) occurs in the presence of an antioxidant and with a nitrogen purge of the liquid formulations and the headspace of vials containing the liquid formulation during manufacture. The optimal pH may depend upon the nature of the antioxidant used as well as the physical properties of the propofol (see 58-65). Thompson et al. further disclose that propofol is also subject to light catalyzed degradation. Therefore, the liquid formulation is generally stored in a light-resistant or lightproof container. Suitable containers, such as vials, bottles, syringes or ampoules, can be made of amber-colored glass, light-blocking plastic, or paper, plastic, foil, metal or otherwise covered glass and/or plastic. The combined use of an antioxidant, light-resistant or lightproof container and an oxygen-free or oxygen-reduced environment provides the greatest protection against degradation of the propofol (see col. 23, lines 41-50). The propofol is generally present in amounts ranging from about 0.1% to 5% by weight or more preferably 1% to 2% by wt. of propofol based upon the total weight of the formulation (see col 19, lines 9-12). Dosage levels of propofol for producing general anesthesia, both induction (for example about 2.0 2.5 mg/kg of body weight for an adult) and maintenance (for example about 4 12 mg/kg of body weight/hr), and for producing a sedative effect (for example, 0.3 4.5 mg/kg of body weight/hr), may be derived from the substantial literature on propofol. Furthermore, the anesthetist and/or physician would modify the dose to achieve the desired effect in a patient in accordance with the conventional skill in the art (see col. 19, lines 13-22). the term "acidifying agent" is intended to mean a compound used to provide an acidic medium for product stability. Such compounds include, by way of example and without limitation, acetic acid, acidic amino acids, **citric acid**, fumaric acid and other alpha hydroxy acids, hydrochloric acid, ascorbic acid, phosphoric acid, sulfuric acid, tartaric acid and nitric acid and others known to those of ordinary skill in the art (see col. 20, lines 27-35). The term "buffering agent" is intended to mean a compound used to resist change in pH upon dilution or addition of acid or alkali. Such compounds include, by way of example and without limitation, acetic acid, sodium acetate, adipic acid, benzoic acid, sodium benzoate, citric acid, maleic acid, monobasic sodium phosphate, dibasic sodium phosphate, lactic acid, tartaric acid, potassium metaphosphate, potassium phosphate, monobasic sodium acetate, sodium bicarbonate, sodium tartrate and sodium citrate anhydrous and dihydrate and others known to those of ordinary skill in the art (see col. 20, lines 64-67 and col. 21, lines 1-7). The liquid formulation can include a buffering agent, acidifying agent, alkalizing agent or combination thereof as a means of controlling the pH of the liquid. The pH of the liquid formulation will generally range from about 4.5 9.5. In one embodiment, the pH of the liquid formulation approximates the pH of blood or plasma. Exemplary buffering agents, acidifying agents and alkalizing agents are disclosed herein. In one embodiment, the buffering agent is a phosphate or citrate buffer present at a concentration of about 0.01 M of the liquid formulation, with a pH of 5.0 to 7.5 (see col. 23, lines 14-25). Suitable hydroxy acids include by way of example, and without limitation, **citric acid**, malic acid, lactic acid, and tartaric acid and others known to those of ordinary skill in the art (see col. 21, lines 40-43). The term "emulsifier" or "emulsifying agent" is intended to mean a compound added to one or more of the phase components of an emulsion for the purpose of stabilizing the droplets of the internal phase within the external phase. Such compounds include, by way of example and without limitation, lecithin, polyoxylethylene-polyoxypropylene ethers, polyoxylethylene-sorbitan monolaurate, polysorbates, sorbitan esters, stearyl alcohol, tyloxapol, tragacanth, xanthan gum, acacia, agar, alginic acid, sodium alginate, bentonite, carbomer, carboxymethyl cellulose sodium, cholesterol, gelatin, hydroxyethyl cellulose, hydroxypropyl cellulose, octoxynol, oleyl alcohol, polyvinyl alcohol, povidone, propylene glycol monostearate, sodium lauryl sulfate, and others known to those of ordinary skill in the art (see col. 22, lines 22-37). The dosage form of the invention can also include oils, for example, fixed oils, such as peanut oil, sesame oil, cottonseed oil, corn oil and olive oil; fatty acids, such as oleic acid, stearic acid and isostearic acid; and fatty acid esters, such as ethyl oleate, isopropyl myristate, fatty acid glycerides and acetylated fatty acid glycerides. It can also include alcohols, such as ethanol, isopropanol, hexadecyl alcohol, glycerol and propylene glycol; glycerol ketals, such as 2,2-dimethyl-1,3-dioxolane-4-methanol; ethers, such as poly(ethylene glycol) 450; with petroleum hydrocarbons, such as mineral oil and petrolatum; water; or with mixtures thereof; with or without the addition of a pharmaceutically suitable surfactant, suspending agent or emulsifying agent (see col. 19, lines 56-67 and col. 20, lines 1-2). The formulation of the present invention can include a preservative, antioxidant, buffering agent, acidifying agent, alkalizing agent, **antibacterial agent**, antifungal agent, solubility enhancing agent, complexation enhancing agent, solvent, electrolyte, salt, water, stabilizer, tonicity modifier, antifoaming agent, oil, emulsifying agent, bulking agent, cryoprotectant or a combination thereof (see col. 20, lines 10-17).

Chen et al. teach the present invention is directed to a pharmaceutical omposition including a hydrophobic therapeutic agent having at least one ionizable functional group, and a carrier. The carrier includes an ionizing agent capable of ionizing the functional group, a surfactant, and optionally solubilizers, triglycerides, and neutralizing agents. The invention further relates to a method of preparing such compositions by providing a composition of an ionizable hydrophobic therapeutic agent, an ionizing agent, and a surfactant, and neutralizing a portion of the ionizing agent with a neutralizing agent. The compositions of the invention are particularly suitable for use in oral dosage forms (see abstract). Also included as oils in this category of surfactants are oil-soluble vitamins, such as vitamins A, D, E, K, etc. Thus, derivatives of these vitamins, such as **tocopheryl PEG-1000 succinate** (TPGS, available from Eastman), are also suitable surfactants (see col. 19, lines 52-56). Examples of suitable surfactants of this class are shown in Table 15. Since the compounds are widely available, commercial sources are not listed in the Table. The compounds are listed by generic name, Poloxamer 237 (see col. 26, lines 18). Table 18 sodium deoxycholate example for an ionic surfactant (see col. 27, line 60). Several particularly preferred carrier compositions are those which PEG-20 laurate, PEG-32 laurate, PEG-32 dilaurate, PEG-12 oleate, PEG-15 oleate, PEG-20 oleate, PEG-20 dioleate, PEG-32 oleate, PEG-200 oleate, PEG-400 oleate, PEG-15 stearate, PEG-32 distearate, **PEG-40 stearate** (see col. 29, lines 35-42). Among these preferred surfactants, more preferred are PEG-20 laurate, PEG-20 oleate, PEG-35 castor oil, PEG-40 palm kernel oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, polyglyceryl-10 laurate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, PEG-30 cholesterol, polysorbate 20, polysorbate 80, POE-9 lauryl ether, POE-23 lauryl ether, POE-10 oleyl ether, PEG-24 cholesterol, sucrose monostearate, sucrose monolaurate and poloxamers. Most preferred are PEG-35 castor oil, PEG-40 hydrogenated castor oil, PEG-60 corn oil, PEG-25 glyceryl trioleate, PEG-6 caprate/caprylate glycerides, PEG-8 caprate/caprylate glycerides, polysorbate 20, polysorbate 80, **tocopheryl PEG-1000 succinate,** PEG-24 cholesterol, and hydrophilic poloxamers (see col. 30, line 8). Among the specifically preferred hydrophobic surfactants, most preferred are oleic acid; lauric acid; glyceryl monocaprate; glyceryl monocaprylate; glyceryl monolaurate; glyceryl monooleate; glyceryl dicaprate; glyceryl dicaprylate; glyceryl dilaurate; glyceryl dioleate; acetylated monoglycerides; propylene glycol oleate; propylene glycol laurate; polyglyceryl-3 oleate; polyglyceryl-6 dioleate; PEG-6 corn oil; PEG-20 corn oil; PEG-20 almond oil; **sorbitan monooleate**; sorbitan monolaurate; POE-4 lauryl ether; POE-3 oleyl ether; ethyl oleate; and **poloxamers** (see col. 31, lines 16-25). Also preferred are mixtures of at least one hydrophilic surfactant and at least one hydrophobic surfactant. The surfactant or surfactant mixture is present in an amount sufficient to promote the continued solubilization of the therapeutic agent in the gastrointestinal tract. Although small amounts of surfactant may provide some stabilization of the solubilized herapeutic agent, it is presently preferred to include a surfactant in an amount of at least about 10%, preferably about 20-90% by weight, based on the total weight of the composition. Also preferred are mixtures of surfactants, wherein the total amount of surfactant is at least about 10%, and preferably about 20-90% by weight, based on the total weight of the composition (see col. 31, lines 28-39).

Clearly, one having ordinary skill in the art would have been motivated to use the teachings of Thompson et al. for the preparation of propofol. Both Chen et al. and Thompson et al. provide the skilled asrtisan with choices of surfactant, ionizing agents, and neutralizing agents, etc., and any additional component needed for the formulation. As combined, the teachings of Thompson et al. for making an injectable formulation taken with the teachings of Chen et al. that discloses specific surfactant.

It would have been obvious to one having ordinary skill in the art at the time the invention was made to have modified the teachings of the above references and produce a pharmaceutical formulation for an injectable drug such as propofol.

Thus the claimed invention was within the ordinary skill in the art to make and use at the time the claimed invention was made and as a whole, prima facie obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zohreh Vakili whose telephone number is 571-272-3099. The examiner can normally be reached on 8:30-5:00 Mon.-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Zohreh Vakili

Patent Examiner
1614

June 13, 2007

6/25/07
ARDIN H. MARSCHEL
SUPERVISORY PATENT EXAMINER